REMARKS

Status Summary

Claims 47, 51-65, and 68 are pending. The rejection of claim 64 under 35 U.S.C. §112, first paragraph, as allegedly presenting new matter is withdrawn. Claims 47, 51-65, and 68 remain rejected under the judicially created obviousness-type double patenting over U.S. Patent No. 6,998,125. Claims 47, 51-63, 65 and 68 remain rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,695,770 ("Raychaudhuri") in view of Woodworth et al. (1996) *Cell Growth & Differentiation* 7:811-820 ("Woodworth"), PCT International Publication No. WO 94/09815 ("Segarini"), as evidenced by Schmolka et al. (1977) *J. Am. Oil Chem. Soc.* 54:110-116 ("Schmolka"), for claims wherein the TGFβ antagonist is an anti-TGFβ antibody.

Claims 47, 51-63, 65 and 68 remain further rejected under 35 U.S.C. §103(a) as allegedly obvious over Raychaudhuri in view of Woodworth and Segarini, as evidenced by Schmolka, Schultz-Cherry et al. (1995) *J. Biol. Chem.* 270(13):7304-10 ("Schultz-Cherry"), and/or PCT International Publication No. WO 91/08298 ("Capon") for claims wherein the TGFβ antagonist is a TGFβ receptor Fc-fusion protein or a thrombospondin peptide that binds to TGFβ and inhibits TGFβ activity. Claim 64 is rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Claim 47 is amended to specify that administration of the antigen-containing adjuvant formulation and the at least one agent elicits a synergized cytotoxic T cell lymphocyte response against cervical cancer cells in a patient. Support for this amendment lies in the specification at least at page 6, line 6-13. Claim 64 is cancelled.

Reconsideration is respectfully requested in view of the foregoing amendment and following remarks.

Rejection of Claims Under The Doctrine of

Nonstatutory Obviousness Type Double Patenting

The rejection of claims 47, 51-65, and 68 under the doctrine of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-2 and 4-19 of U.S. Patent No. 6,998,125 is maintained. Official action, page 3. In response to this rejection, the applicants maintain that a terminal disclaimer will be considered when one or more claims of the present application are in condition for allowance.

Rejection of Claims Under 35 U.S.C. §103(a)

Based Upon Raychaudhuri, Woodworth, Segarini, and Schmolka

Claims 47, 51-63, 65, and 68 remain rejected under 35 U.S.C. §103(a) as allegedly obvious over Raychaudhuri in view of Woodworth and Segarini et al., as evidenced by Schmolka to the extent that the TGFβ antagonist set forth in the claimed methods is an anti-TGFβ antibody. Official action, page 3.

The rationale for the examiner's rejections have been set forth and discussed previously. The examiner further notes that the Ozbun article cited in the applicants' previous response was not received by the office, that the applicant has argued limitations not found in the claims, and that a skilled artisan would have a reasonable expectation of arriving at the claimed methods in view of the teachings of the cited prior art.

The burden is on the examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc.*, 550 U.S. __, 82 USPQ2d 1385 (2007), the U.S. Supreme Court affirmed that this analysis includes the following factual inquiries: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art.

The Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* ("USPTO Guidelines") state that, having undertaken the factual inquiries of *Graham*, a rejection under 35

U.S.C. §103 may be supported by one or more of the following rationales: (1) combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of a known technique to improve similar devices in the same way; (4) applying a known technique to a known device ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (5) variations that would have been predictable to one of ordinary skill in the art; and (6) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention. 72 Fed. Reg. 57526, at 57529 (October 10, 2007).

Each of the above-noted rationales requires predictability in the art and/or a reasonable expectation of success, and the examiner must consider objective evidence which rebuts such predictability and reasonable expectation of success. This objective evidence or secondary considerations may include unexpected results and/or failure of others (*e.g.*, evidence teaching away from the currently claimed invention), evidence of commercial success, and long-felt but unsolved needs, as found in the specification as-filed or other source. *Id*. When considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at __, 82 USPQ2d at 1396.

The applicants submit that the examiner fails to make a *prima facie* case of obviousness because the factual inquiries set forth in *Graham v. John Deere Co*. have not been considered. Having undertaken such an objective analysis, the applicants further submit that the cited references fail to render the present claims obvious given that:

(1) the instant invention provides a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cervical cancer cells in a patient in need thereof, comprising administering:

(a) an antigen-containing adjuvant formulation, the formulation comprising a human papillomavirus E7 protein that is capable of inducing a cytotoxic T cell lymphocyte response specific for the human papillomavirus E7 protein; and

(b) a therapeutically effective amount of at least one agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing

activation of transforming growth factor-β (TGFβ) selected from the group consisting of an anti-TGFβ antibody, a TGFβ receptor-fusion protein, a TGFβ receptor Fc-fusion protein, an anti-TGFβ receptor antibody that blocks the interaction of TGFβ and TGFβ receptor, and a thrombospondin peptide that binds to TGFβ and inhibits TGFβ activity, wherein the combination of the antigen-containing adjuvant formulation and the at least one agent elicits a synergized cytotoxic T cell lymphocyte response against cervical cancer cells in a patient;

(2) the scope and content of the prior art did not describe such a method; and

(3) at the time of the instant invention, one of ordinary skill in the pertinent art would not have reasonably concluded that the claimed methods could be performed with a reasonable chance of success given the conflicting data on TGFβ, *i.e.*, specifically that TGFβ can either promote or inhibit proliferation of HPV-positive keratinocytes, and TGFβ inhibits proliferation of cervical cancer cells. *See* Ozbun et al., *J. Virol.* 70(8):5437-5446 (1996) (discussed further below and submitted herewith).

In addition, the applicants assert that claims 47, 51-63, 65, and 68 are not rendered obvious by the cited references because the rationales explicitly provided by the USPTO Guidelines, or other rationales forming the basis of an obviousness-type rejection, require predictability in the art and/or a reasonable expectation of success, which is lacking from the teachings of the cited references as described further below.

As discussed above, claim 47 is amended to set forth a method for enhancing an antigen-specific cytotoxic T cell lymphocyte response against cervical cancer cells in a patient in need thereof, comprising administering an antigen-containing adjuvant formulation, the formulation comprising a human papillomavirus E7 protein that is capable of inducing a cytotoxic T cell lymphocyte response specific for the human papillomavirus E7 protein, and a therapeutically effective amount of at least one agent that is capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor-β (TGFβ) selected from the group consisting of an anti-TGFβ antibody, a TGFβ receptor-fusion protein, a TGFβ receptor Fc-fusion protein, an anti-TGFβ receptor antibody that blocks the interaction of TGFβ and TGFβ receptor, and a thrombospondin peptide that binds to TGFβ and inhibits TGFβ

activity, wherein administration of the antigen-containing adjuvant formulation and the at least one agent elicits a synergized cytotoxic T cell lymphocyte response against cervical cancer cells in a patient.

As previously acknowledged by the examiner, Raychaudhuri does not teach a method for enhancing an antigen-specific CTL response that includes administration of an agent capable of neutralizing, blocking, antagonizing, or down regulating the activity or preventing activation of transforming growth factor-β (TGFβ). To account for this deficiency, the examiner alleges that Woodworth teaches the skilled artisan that TGFβ1 stimulates the growth of HPV-immortalized keratinocytes and that Segarini teaches that TGFβ can cause immunosuppression, that administration of an anti-TGFβ antibody can counteract this immunosuppression (*see* page 2, second paragraph), and that administration of a TGFβ-binding receptor fragment can increase the effectiveness of a vaccine (*see* page 6).

However, prior to the instant disclosure, as evidenced by Ozbun et al., one of ordinary skill in the art appreciated that TGFβ could either promote or inhibit proliferation of HPV-positive keratinocytes, and that TGFβ inhibits proliferation of cervical cancer cells. The examiner has discounted this assertion, because the previously submitted supporting abstracts allegedly did not provide or support evidence that TGFβ inhibits growth of HPV-immortalized cells under conditions that induce squamous differentiation (and the examiner alleges that Woodworth clearly teaches that conditions that induce squamous differentiation are necessary for growth induction by TGFβ).

Accordingly, the applicants submit the full text of Ozbun et al herewith. This reference discloses that TGFβ induces HPV-positive keratinocytes and cervical cancer cells to differentiate in a tissue culture system that models conditions *in vivo* and under conditions that support differentiation (*i.e.*, "an organotypic tissue culture system which emulates the three-dimensional architecture and differentiation scheme of keratinocytes in vivo" {pg. 5438, column 1}). As asserted previously, these results are *directly opposite* to those of Woodworth. In view of such conflicting results, one of skill in the art would not readily conclude that the presently claimed combination methods could be performed with a reasonable chance of success.

Moreover, when considering the combined teachings of Raychaudhuri, Ozbun, and Segarini, one skilled in the art would have considered that this combination of references,

available at the time of the instant invention, actually *teaches away* from the claimed methods. A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by applicant" *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). Based upon Ozbun, one skilled in the art would have been discouraged from using an inhibitor of TGFβ activation to thereby elicit an anti-tumor response, given that Ozbun teaches a role for TGFβ in induction of cervical cancer cell differentiation.

The USPTO Guidelines also direct the examiner to consider rebuttal evidence (see "V. Consideration of Applicant's Rebuttal Evidence"). Suitable rebuttal evidence in accordance with the Guidelines include (a) the results of the claimed combination were unexpected and (b) the elements in combination do not merely perform the function that each element performs separately (see V(3) and V(2) respectively). The applicants submit that, in view of the prior art, the results obtained by the claimed methods were certainly unexpected, as one of ordinary skill in the art would question the operability of administering the claimed antigen-containing adjuvant formulation and the at least one agent to elicit a cytotoxic T cell lymphocyte response against cervical cancer cells in a patient.

Furthermore, the results of the combination are not only unpredictable in view of the prior art, but, as evidenced by the results in Figures 2A and 2B of the present application, the antigen-containing adjuvant formulation and the at least one agent in combination do not merely perform the function that each element performs separately. Unexpectedly, the combination elicits a synergized cytotoxic T cell lymphocyte response against cervical cancer cells in a patient. Given that CTL-inducing formulations and agents for inhibition of TGFβ immunosuppression have distinct biological effects based upon modulation of different cellular functions, there is no way this synergistic effect could have reasonably been predicted. At best, a skilled artisan would predict an additive effect, absent the data of Ozbun and like references that teach away from the claimed methods.

The synergistic effect of a CTL-inducing antigen formulation in combination with an inhibitor of TGFβ activation, as presently claimed, could only be known once experimental evidence demonstrating such responses was available, as first disclosed in the instant

application. In particular, Figures 2A-2B demonstrate the anti-tumor activity of E7-PROVAX® when used in combination with an inhibitory anti-TGFβ antibody. Figure 2A shows that administration of E7-PROVAX® had no effect on tumor growth, *i.e.*, the response closely tracked that of tumor-bearing animals that received no treatment (control). Likewise, administration of an inhibitory anti-TGFβ antibody showed a minimal anti-tumor response that also closely tracked the control. By contrast, animals receiving both agents showed marked inhibition of tumor growth. Thus, a previously inactive single agent, E7-PROVAX®, was rendered effective by use in combination with a second agent, an anti-TGFβ antibody. The outcome of the combined treatment is synergistic or greater than additive, *i.e.*, more than the sum of zero effect (the effect of E7-PROVAX® as a single agent) plus the effect of the inhibitory anti-TGFβ antibody. Figure 2B shows similar results. The effect of repeated administration of an anti-TGFβ antibody increases its anti-tumor response, however, the combined effect of E7-PROVAX® plus anti-TGFβ antibody is still synergistic or greater than additive. As required to support a showing of non-obviousness, the evidence relied on by the applicant upon establishes "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) MPEP §716.02(b) I.

Based upon the foregoing, the cited references do not establish a *prima facie* case of obviousness, and the applicants respectfully request that the rejection of claims 47, 51-63, 65, and 68 under 35 U.S.C. §103(a) as allegedly being unpatentable over Raychaudhuri in view of Woodworth and Segarini, and as evidenced by Schmolka, be withdrawn.

Rejection of Claims Under 35 U.S.C. §103(a)

Based Upon Raychaudhuri, Woodworth, Segarini, Schmolka, Schultz-Cherry, and Capon

Claims 47, 51-63, 65, and 68 remain rejected under 35 U.S.C. §103(a) as allegedly obvious over Raychaudhuri in view of Woodworth and Segarini, as evidenced by Schmolka and further in view of Schultz-Cherry or Capon to the extent that the TGFβ antagonist set forth in the claimed methods is a TGFβ receptor Fc-fusion protein or a thrombospondin peptide that binds to TGFβ and inhibits TGFβ activity (*e.g.*, GGWSHW). Official action, page 6.

The examiner alleges that the claimed inventions are obvious for the reasons discussed *supra*, and that, in further view of the thrombospondin peptide GGWSHW disclosed by Schultz-Cherry or a TGFβ receptor Fc-fusion protein disclosed by Capon, one of ordinary skill in the art could increase the versatility of the treatment methods alleged by the examiner to be suggested by the combined teachings of Raychaudhuri, Woodworth, Segarini, and Schmolka.

As discussed above, the combined teachings of Raychaudhuri, Woodworth, Segarini, and Schmolka fail to establish the obviousness of the claimed methods, because (briefly summarizing the response above) a) one of skill in the art would not readily conclude that the presently claimed combination methods could be performed with a reasonable chance of success, b) the combined teachings of Raychaudhuri, Woodworth, Segarini, and Schmolka teach away from the claimed methods, c) the results of the claimed methods were unexpected, and d) the combination of the antigen-containing adjuvant formulation and the at least one agent do not merely perform the function that each performs separately, but rather elicit a synergized CTL response against cervical cancer cells in a patient.

The failure of the cited references to establish a *prima facie* case of obviousness is not remedied by the additional teachings of Schultz-Cherry and/or Capon. These references describe additional TGFβ inhibitors, but lack any teaching, suggestion, or motivation to combine such agents with an antigen formulation for administration to a patient having cervical cancer. The applicants therefore respectfully request that the rejection of claims 47, 51-63, 65, and 68 under 35 U.S.C. §103(a), as allegedly unpatentable in view of Raychaudhuri, Woodworth, Segarini, Schmolka, Schultz-Cherry, and/or Capon be withdrawn.

35 U.S.C. §112, Second Paragraph, Indefiniteness

Claim 64 is rejected under 35 U.S.C. §112, second paragraph, because the phrase "low levels of an immunostimulating peptide" is allegedly indefinite. In order to expedite prosecution, claim 64 is canceled, rendering this rejection moot.

CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, she is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date: 29 January 2008

By /thomas a cawley jr/
Thomas A. Cawley, Jr., Ph.D.
Reg. No. 40,944

PILLSBURY WINTHROP SHAW PITTMAN LLP
P.O. Box 10500
McLean, VA 22102
Tel. No. 703-770-7900
Direct Dial 703.770.7944
Fax No. 703.770.7901